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Micronutrient supplementation during pregnancy and the risk of pregnancy-induced hypertension: A randomized clinical trial☆

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SUMMARY

Background & aims: Increasing evidence suggests that iron-containing multiple micronutrient may reduce the risk of pregnancy-induced hypertension including gestational hypertension or preeclampsia. We aimed to examine whether 30 mg iron plus folic acid or multiple micronutrients during pregnancy reduces the risk of pregnancy-induced hypertension.

Methods: We conducted a secondary data analysis by the dataset from a double-blind randomized controlled trial in China from 2006 to 2009 that was conducted to investigate the effects of multiple micronutrient supplements on adverse pregnancy outcomes when provided to pregnant women with no/mild anemia. We used logistic regression to estimate the adjusted odds ratio and 95% confidence interval and test for effect modification.

Results: The incidence of pregnancy-induced hypertension was 7.1% (423/5923), 6.3% (374/5933) and 6.3% (372/5914) among the pregnant women who took folic acid only, iron-folic acid and multiple micronutrient supplements, respectively. The adjusted odds ratios associated with iron-folic acid supplements and multiple micronutrient supplements for pregnancy-induced hypertension were both nearly 0.88 (95% confidence interval, 0.76–1.02), compared with folic acid supplements only. Among pregnant women aged 20–24 years, iron-folic acid (adjusted

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Statement of authorship

Sen Chen and Nan Li contributed equally to this manuscript. Sen Chen and Nan Li had full access to all of the study's data and takes complete responsibility for the accuracy of the data analysis. Study concept and design: Sen Chen, Nan Li, Mei, and Ye. Acquisition of data: Sen Chen, Nan Li, Mei, and Liu. Interpretation of data: Sen Chen, Nan Li, Mei, Zhiwen Li, Liu, and Serdula. Drafting of the manuscript: Sen Chen, Nan Li, and Mei. Critical revision of the manuscript: Sen Chen, Nan Li, Mei, Ye, Zhiwen Li, and Serdula. Statistical analysis: Sen Chen, Nan Li, and Mei. Obtained funding: Sen Chen, Nan Li, Mei, and Ye. Administrative and technical support: Sen Chen, Nan Li, Mei, Zhiwen Li, and Ye. Study supervision: Mei, Ye and Serdula.

Conflict of interest

All authors read and approved the final manuscript and do not declare any conflict of interest or competing interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.01.029.

odds ratios: 0.81, 95% confidence interval: 0.67–0.96) or multiple micronutrient supplementation (adjusted odds ratios: 0.83, 95% confidence interval: 0.70–0.99) can significantly reduce the risk of pregnancy-induced hypertension compared to folic acid supplementation.

Conclusions: Overall, there were no significant differences in pregnancy-induced hypertension across supplement groups. However, among pregnant women aged 20–24 years, iron-containing multiple micronutrient supplementation was associated with a reduced risk of pregnancy-induced hypertension compared with folic acid supplements only.

Trial registration: ClinicalTrials.gov NCT00133744.

Keywords

Micronutrient supplementation; Folic acid; Iron; Pregnancy-induced hypertension; Randomized clinical trial

1. Introduction

Hypertension complicates 5%–7% of all pregnancies [1]. Pregnancy-induced hypertension (PIH) is defined as hypertension starting after 20 weeks of gestation with or without proteinuria, including gestational hypertension and preeclampsia [2]. Women with PIH are at higher risk for cesarean delivery, placental abruption, renal dysfunction, and subsequent cardiovascular morbidity [3,4]; related risks to the fetus include fetal growth restriction [5], preterm delivery [6], and low birth weight. Many studies have been conducted to explain and predict PIH, but, thus far, the cause of PIH remains largely unknown [7].

Previous studies suggest that oxidative stress and endothelial cell dysfunction are associated with the development of preeclampsia [8]. Low serum antioxidant levels are also correlated with increased oxidative stress and endothelial cell dysfunction [9]. Dietary antioxidant supplements, such as Vitamin C and E [10], copper [11], zinc [12], and selenium [13], have been associated with reduced oxidative stress and improved endothelial function. Vitamin B_{12} intake reduces serum homocysteine which has also been associated with hypertension in pregnancy [14]. It is plausible that multiple micronutrient (MMN) supplements reduce the risk of PIH. Some studies suggested that MMN supplements could reduce the risk of PIH compared with iron-folic acid (IFA) supplements or no supplements [15], however a clinical trial in Mexico found that antioxidant vitamins alone did not have a protective effect for prevention of preeclampsia [16].

In addition, both iron deficiency [17] and elevated serum iron [18,19] are suspected to be associated with oxidative stress; however, study findings have been inconsistent. Some case–control studies indicate that serum iron status is higher in hypertensive pregnant women compared to normotensive pregnant women [11,20]; however, other studies have come to the opposite conclusion [21,22]. A small randomized placebo-controlled trial among pregnant women with elevated hemoglobin (≥13.2 g/dL) found that hypertension was increased in the daily iron (50 mg) supplementation compared to the placebo group [23]. To our knowledge, there has been no large randomized control trial which evaluates the effect of iron supplementation on PIH in a healthy population of women with no or mild anemia.

In a randomized double-blind controlled trial in China, we enrolled pregnant women to examine the effect of FA, IFA, or MMN supplements on perinatal mortality (primary outcomes) and the other maternal and infant health outcomes. The results of this study were reported earlier [24,25]. The current study aim to investigate the association of supplements containing IFA, MMN, and FA with overall PIH, early onset, and late onset PIH. In addition, we also investigated the potential modifying effect of hemoglobin status and other factors on the association of supplement groups with PIH.

2. Materials and methods

2.1. Background and original study

From May 2006 to April 2009, 18,775 nulliparous pregnant women were enrolled from 5 counties in northern China. All women were enrolled in the trial before 20 weeks of gestation. All pregnant women were at least 20 years old and had not consumed micronutrient supplements other than folic acid in the prior 6 months. We measured hemoglobin at enrollment and excluded those with hemoglobin level <10.0 g/dL. All the participants recorded their menstrual period 2 or more months before enrollment. Gestational ages were calculated based on the date of last menstrual period.

Women were randomly assigned to the FA group (400 μg folic acid), IFA group (400 μg folic acid and 30 mg iron), or MMN group (400 μg folic acid, 30 mg iron, and 13 additional vitamins and minerals) and were advised to consume one pill every day from enrollment to delivery. Local health workers visited each woman monthly to collect information about the women's capsule-taking, counted the left over pills, and filled out a capsule-taking form. Compliance was defined as the number of supplements consumed divided by the total number of days between initiation and termination of supplementation; the number of supplements used was derived from the number of supplements remaining in the bottle at each return visit. All the subjects gave informed consent.

2.2. Definition of PIH

Pregnant women were advised to make prenatal visits at least 1 time in the first trimester, monthly in the second trimester, every other week from 28 weeks to 36 weeks and weekly after 36 weeks. Using a mercury sphygmomanometer, blood pressure was measured during routine antenal care visits by specifically trained local health workers. Appropriate-sized cuff bladder was determined at each visit based on arm circumference of each participant. Blood pressure was measured in the right arm with a standard mercury sphygmomanometer device, and its value was observed on 2 or more consecutive occasions with an interval of ≥2 min. Data were collected and inputted into the computerized perinatal monitoring system by local health workers. Pregnancy-induced hypertension (PIH) was defined as any occurrence of either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg starting at or after 20 weeks of gestation among women with previously normal blood pressure prior to 20 weeks [2,26]. Severe PIH was defined as the presence of systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg [27]. PIH was also classified into 2 types: early onset (onset at 20–28 weeks of gestation) and late onset (onset at ≥ 28 weeks of gestation) [28].

2.3. Statistical analysis

To be included in the analysis, participants had to have at least one blood pressure measurement before and one after 20 weeks. Any woman with one high BP measurement prior to 20 weeks was excluded from all analyses. To be eligible for the sub-analysis of early onset PIH, each woman had to have blood pressure measured before 20 weeks of gestation and between 20 and 28 weeks of gestation. For the analysis of late onset PIH, each woman had to have blood pressure measured during the first two time periods and after 28 weeks of gestation. Women who were found to have early onset hypertension were also excluded from analysis of late onset hypertension.

All analyses were carried out according to an intent-to-treat principle. We performed the test in distribution of baseline characteristics among the 3 supplement groups using χ^2 tests for categorical variables including maternal age (20–24, 25–29, ≥30 years), body mass index (BMI) (<18.5, 18.5–24.9, ≥25 kg/m^2), ethnicity (Han, other), education (primary school or lower, secondary, high school or higher), occupation (farmer, other), gestational week (<12, ≥12 weeks), hemoglobin level at first prenatal visit (<13.2, ≥13.2 g/dL) and mild anemia (hemoglobin of 100–109 g/L) [25]. We also examined the distribution of above baseline characteristics between the participants removed from analysis and the remaining participants. Because PIH was uncommon in our population, odds ratios (ORs) were used to approximate risk ratios. Unadjusted ORs with 95% confidence intervals (CIs) for hypertension outcomes (all PIH, severe PIH, early onset PIH and late onset PIH) were calculated using logistic regression. All three comparisons (IFA vs FA, MMN vs FA, MMN vs IFA) were conducted in one model with contrast statements. An unconditioned logistic regression model was used to adjust for the main covariates, including maternal age, gestational age at enrollment, ethnicity, education, occupation, BMI at first prenatal visit, hemoglobin level at first prenatal visit, and compliance (<80%, 80%–90%, ≥90%).

To examine effect modification, we added interaction terms between supplement groups and each covariate one at a time. Next we added all covariates and all significant interaction terms to the model and performed backward elimination of two way interaction terms. Finally, interaction terms for three covariates (maternal age, education and hemoglobin level at first prenatal visit) were retained in the final model because they were significant. For each covariate with a significant interaction we conducted a stratified analysis. For each stratification, we used one multiple regression model with all covariates with a contrast statement. Results were considered statistically significant with a two-sided $P < 0.05$ except for interactions which were considered statistically significant with a two-sided $P < 0.10$. All data were analyzed by using the SPSS (v.20.0) software.

2.4. Trial registration and ethical approval

This trial was registered at clinicaltrials.gov as NCT00137744. The study protocol was approved by the institutional review boards of the Centers for Disease Control and Prevention, Atlanta, Georgia, and Peking University, Beijing, China.

3. Results

Among the 18,775 women enrolled in the original study, 28 (0.2%) moved, 33 (0.2%) dropped out, 2 died during pregnancy and 548 (2.9%) had spontaneous or induced abortions before 20 weeks. Of the 18,164 (96.8%) remaining women, we excluded 285 (1.5%) because they did not have at least one blood pressure assessment before and after 20 weeks of gestation and 109 (0.6%) women with one high BP prior to 20 weeks, leaving a total of 17,770 (95.7%) women for analysis of overall PIH.

In regard to analysis of early onset PIH, 978 women were additionally excluded because they did not have blood pressure measured between 20 and 28 weeks of gestation leaving a total of 16,792 women (89.4% of 18,775); in regard to late onset PIH, 78 were excluded because they had early onset PIH and 1109 women were excluded because they had no blood pressure measurement at 20–28 weeks gestation and/or no measurement after 28 weeks of gestation leaving a total of 16,583 women (88.3% of 18,775).

Of the 17 770 women included in the analysis of overall PIH, 5923 (33.3%) took folic acid supplements (FA group), 5933 (33.4%) took iron-folic acid supplements (IFA group) and 5914 (33.3%) took multiple micronutrient supplements (MMN group). Table 1 showed that women in the 3 intervention groups, FA, IFA and MMN, had similar baseline characteristics. The mean (SD) maternal age, BMI and gestational age at enrollment were 23.6 (2.8) years, 22.3 (2.8) kg/m^2, and 12.0 (4.5) weeks, respectively. Almost all of the participants were from race of Han, 1.6% had primary or less education, and 91.0% were farmers. The mean compliance was 93.3%, 92.9% and 91.6% in the FA, IFA and MMN groups, respectively. The women included in this analysis had blood pressure measured an average of 7.2 (SD value = 2.5) times from 20 weeks gestation to delivery. There was no significant difference among the three groups in regard to times of BP measurements (data not shown).

Of 17 770 women, 1169 (6.6%) were diagnosed with PIH. The incidence of PIH was 7.1% in the FA group, 6.3% in the IFA group, and 6.3% in the MMN group (Table 2). Compared to the FA group, the adjusted ORs of PIH for the IFA group and MMN group were 0.88 (95% CI 0.76–1.02) and 0.88 (95%CI 0.76–1.02).

Of 17,770 women, 0.5% were diagnosed with severe PIH. Of 16,792 women, 0.5% were diagnosed with early onset PIH. The ORs of severe PIH and early onset PIH were not significantly different by supplement group. Of 16,583 women, 6.2% were diagnosed with late onset PIH. Compared to FA alone, the crude OR for late onset hypertension was significantly lower in MMN group (OR = 0.85, 95% CI 0.73–0.99), but the adjusted OR was not significant (OR = 0.86, 95% CI 0.73–1.00). There was no statistical difference in other comparisons.

There was significant effect modification of PIH and supplement group by maternal age ($P_{interaction}$ = 0.016), education (P = 0.014) and hemoglobin level (P = 0.036). No other covariates showed significant effect modification. After stratification by maternal age, we found that, among younger women (20–24 years of age), those who took IFA (OR = 0.81, 95% CI 0.67–0.96) and MMN (OR = 0.83, 95% CI 0.70–0.99) had a significantly reduced odds of PIH compared with folic acid alone (Table 3). Among women whose education level

was primary school or lower, IFA had a significantly reduced odds of PIH compared with FA (OR = 0.16, 95% CI 0.04–0.71). Among women whose hemoglobin level was greater than 13.2 g/dL, MMN had a significant reduced odds of PIH compared with either FA (OR = 0.69, 95% CI 0.51–0.93) or compared with IFA (OR = 0.71, 95% CI 0.52–0.96).

4. Discussion

In this RCT of nulliparous pregnant women, overall, there were not any significant differences in PIH across supplement groups. For pregnant women whose hemoglobin level was greater than 13.2 g/ dL, MMN was associated with about a 30% reduction in the odds of PIH compared with IFA or with FA. For pregnant women between 20 and 24 years old, IFA and MMN were associated with about a 20% reduction in the odds of PIH compared to FA group.

Several observational studies evaluated the effect of MMN on hypertension or preeclampsia in pregnancy. A cohort study of normal weight pregnant women in Denmark found that regular MMN users (13 kinds of vitamins and minerals including iron) had a 20% reduced risk of preeclampsia compared with nonusers [29]. Another observational study in the US found that regular use of multivitamins was associated with a 45% reduction in preeclampsia risk compared with nonuse [15]. In a clinical trial, conducted among HIV-infected pregnant women, those who received MMN had 38% lower risk of developing hypertension during pregnancy than those who received 400 mg ferrous sulfate and 5 mg folate [30]. A small randomized clinical trial conducted among 30 pregnant women with low antioxidant status found that MMN reduced the risk of PIH compared with IFA [31]. However, another randomized clinical trial in Mexico City suggested that antioxidant vitamins alone did not show a protective effect for prevention of preeclampsia compared with a placebo group. Pooled analysis of randomized controlled trials found that consumption with vitamins C and E were not associated with a reduced risk of preeclampsia or gestational hypertension [10,32]. Thus, the association of antioxidant vitamins with hypertension during pregnancy has been inconsistent between studies. Our results did not show a significant difference in the odds of PIH of either MMN or IFA compared with FA.

Both iron deficiency [17] and elevated hemoglobin [18,19] are hypothesized to be associated with PIH. In a small randomized clinical trial of pregnant women with hemoglobin ≥13.2 g/dL in which all women received 1 mg FA daily, Ziaei et al. found that, compared to placebo, administration of a daily iron (50 mg) supplement during the second trimester and delivery period increased the risk of hypertension in pregnancy [23]. In our study, among the women whose hemoglobin ≥13.2 g/dL, the incidence of PIH in the IFA group was similar to that of the FA group and the incidence of PIH in the MMN group was reduced by about one third compared to women who received either IFA or FA. Thus, among women with high hemoglobin, there was no evidence of an increased risk of PIH in women who received iron-containing supplements compared to those receiving FA alone. After further analysis in women who commenced the study with mild anemia, we did not also find that there was any significant effect, either in total, or in the group who were aged 20–24. To the best of our knowledge, this is the first trial to demonstrate a protective effect of MMN on PIH among women with high hemoglobin and further study is warranted.

Few studies conducted stratified analysis of the effects of micronutrients on PIH by maternal characteristics. In an RCT, Merchant et al. found that multivitamin consumption significantly decreased the risk of preeclampsia among the pregnant women between 20 and 29 years old, but found no effect among women more than 30 years old [30]. Our study also found a reduced odds of PIH among younger women consuming IFA or MMN compared to FA. One potential reason may be that the deficiencies of MMN are more prevalent among younger women [33]. A study in the UK suggested that women ≥24 years old had higher intakes of most nutrients than women ≥24 years old [34]. Another study found that lower education was associated with multiple antioxidant inadequacies [35]. In our study, the protective associations of IFA on PIH tended to be stronger when maternal education level was lower.

One limitation of our study was that we did not collect information on proteinuria or other signs of end-organ involvement including abnormal laboratory tests (elevated serum creatinine), so we could not distinguish gestational hypertension from preeclampsia. In addition, even though the average number of blood pressure measurements was more than 7 for all the women, some abnormal blood pressure measurements may have been missed due to sparse blood pressure assessments for some women. Finally, the generalizability of our study is limited, because the study was carried out among mostly normal weight women with no or mild anemia from rural areas of northern China.

Our study has several strengths. This research was a large randomized, double-blind, controlled trial though this is a post hoc analysis. Supplements consumption was assessed through monthly home visits. The mean compliance was greater than 90% in all supplement groups.

Our study is the first large RCT to examine the effect of FA, IFA and MMN on PIH. Overall, there were not any significant differences in PIH across supplement groups. However, compared to FA, prenatal supplementation with MMN or IFA could reduce risk of PIH in women who were younger and supplementation with IFA was associated with a reduced risk in those less educated. Among women with high hemoglobin, compared either the IFA or FA groups, MNN was associated with a reduced risk of PIH.

We hence propose a nationwide multiple micronutrient supplementations that contains iron to reduce occurrence of PIH, especially for those with lower education status. Together with the data from previous randomized clinical trials, our findings suggest that there will be more further investigations about the effect of specific component of MMN on global public health benefits in future international studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline maternal characteristics at enrollment according to study intervention.

Maternal characteristics	FA (n = 5923)[a]	IFA (n = 5933)[a]	MMN (n = 5914)[a]	Total[a]	*P* value[b]
Maternal age					0.690
20–24 years	4479 (75.6)	4498 (75.8)	4531 (76.6)	13508 (76.0)	
25–29 years	1218 (20.6)	1217 (20.5)	1179 (19.9)	3614 (20.3)	
≥30 years	226 (3.8)	218(3.7)	204 (3.4)	648 (3.6)	
BMI at first prenatal visit					0.968
<18.5 kg/m^2	349 (5.9)	356 (6.0)	349 (5.9)	1054 (5.9)	
18.5-24.9 kg/m^2	4764 (80.4)	4779 (80.5)	4743 (80.2)	14286 (80.4)	
>25 kg/m^2	810 (13.7)	798 (13.5)	822 (13.9)	2430 (13.7)	
gestational age at enrollment					0.529
<12weeks	3127 (52.8)	3078 (51.9)	3120 (52.8)	9325 (52.5)	
>12weeks	2796 (47.2)	2855 (48.1)	2794 (47.2)	8445 (47.5)	
Education					0.793
High school or higher	1089 (18.4)	1057 (17.8)	1068 (18.1)	3214 (18.1)	
Secondary	4745 (80.1)	4775 (80.5)	4758 (80.5)	14278 (80.3)	
Primary school or lower	89 (1.5)	101 (1.7)	88 (1.5)	278 (1.6)	
Occupation					0.646
Farmer	5376 (90.8)	5414 (91.3)	5379 (91.0)	16169 (91.0)	
Other	547 (9.2)	519 (8.7)	535 (9.0)	1601 (9.0)	
Ethnicity					0.680
Han	5850 (98.8)	5870 (98.9)	5847 (98.9)	17567 (98.9)	
Other	73 (1.2)	63 (1.1)	67 (1.1)	203 (1.1)	
Hemoglobin level at first prenatal visit					0.213
<13.2 g/dL	4614 (77.9)	4699 (79.2)	4632 (78.3)	13945 (78.5)	
≥13.2 g/dL	1309 (22.1)	1234 (20.8)	1282 (21.7)	3825 (21.5)	
Compliance of supplementation [c]					<0.001
<80%	360 (6.2)	393 (6.7)	507 (8.7)	1260 (7.2)	
80%–90%	669 (11.5)	647 (11.0)	722 (12.4)	2038 (11.6)	
≥90%	4800 (82.3)	4817 (82.2)	4600 (78.9)	14217 (81.2)	

FA, folic acid; IFA, iron–folic acid; MMN, multiple micronutrient; BMI, body mass index; SD, standard deviation.

[a] Data are expressed as number (percentage) of participants except where noted.

[b] Chi-square tests were used to examine statistical differences in categorical variables and analysis of variance was used to examine differences in means among study groups.

[c] Compliance was defined as the number of supplements consumed divided by the number of days from enrollment to birth; the number of supplements consumed was estimated from the number of supplements remaining in the bottle at each return visit.

Table 2

Pregnancy-Induced Hypertension (PIH) incidence and association with supplementation.

No. of case / Total No. (%)					OR (95% CI)		
Outcomes	**FA**	**IFA**	**MMN**		**IFA vs. FA [Reference: FA]**	**MMN vs. FA [Reference: FA]**	**MMN vs. IFA [Reference: IFA]**
All PIH [a]	423/5923 (7.1)	374/5933 (6.3)	372/5914 (6.3)	**Crude**	0.88 (0.76, 1.01)	0.87 (0.76, 1.01)	1.00 (0.86, 1.16)
				Adjusted [c]	0.88 (0.76, 1.02)	0.88 (0.76, 1.02)	1.00 (0.86, 1.17)
Severe PIH [a]	38/5923 (0.6)	25/5933 (0.4)	28/5914 (0.5)	**Crude**	0.66 (0.40, 1.09)	0.74 (0.45, 1.20)	1.12 (0.66, 1.93)
				Adjusted [c]	0.71 (0.42, 1.20)	0.73 (0.43, 1.23)	1.02 (0.58, 1.80)
Early onset PIH [b]	30/5589 (0.5)	20/5619 (0.4)	28/5584 (0.5)	**Crude**	0.66 (0.38, 1.17)	0.93 (0.56, 1.57)	1.41 (0.79, 2.51)
				Adjusted [c]	0.74 (0.41, 1.32)	1.01 (0.59, 1.72)	1.36 (0.76, 2.43)
Late onset PIH [b]	374/5511 (6.9)	336/5563 (6.0)	322/5509 (5.9)	**Crude**	0.88 (0.76, 1.03)	**0.85 (0.73, 0.99)**	0.96 (0.82, 1.13)
				Adjusted [c]	0.88 (0.76, 1.03)	0.86 (0.73, 1.00)	0.97 (0.83, 1.14)

Bold indicate $p < 0.05$.

FA, folic acid; IFA, iron–folic acid; MMN, multiple micronutrient; PIH, pregnancy-induced hypertension; OR, odds ratio; 95% CI, 95% confidential interval.

[a]The PIH was defined as any occurrence of either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg starting at or after 20 weeks of gestation among women with previously normal blood pressure prior to 20 weeks. Severe PIH was defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg. The total sample was 17 770 for PIH and severe PIH.

[b]Early onset PIH was PIH onset at 20–28 weeks of gestation and late onset was PIH onset at ≥28 weeks of gestation. The total sample was 16 792 for early onset PIH and 16 583 for late onset PIH.

[c]Adjusted for maternal age, gestational age at enrollment, BMI at first prenatal visit, hemoglobin level at first prenatal visit, compliance of supplementation, ethnicity, education and occupation.

Table 3

Pregnancy-Induced Hypertension (PIH) stratified by maternal characteristics.

Maternal characteristics	No.	PIH incidence (%)[a]			AOR (95% CI)[b]		
		FA	IFA	MMN	IFA vs. FA [Reference: FA]	MMN vs. FA [Reference: FA]	MMN vs. IFA [Reference: IFA]
Age group							
20–24 years	13,508	7.1	5.8	5.9	**0.81 (0.67, 0.96)**	**0.83 (0.70, 0.99)**	1.03 (0.86, 1.26)
25–29 years	3614	7.5	7.5	7.6	1.02 (0.75, 1.39)	1.02 (0.75, 1.39)	1.01 (0.74, 1.38)
≥30 years	648	7.1	10.1	8.3	1.46 (0.72, 2.94)	1.12 (0.53, 2.37)	0.78 (0.39, 1.55)
Education							
High school or higher	3214	8.2	7.8	8.2	0.93 (0.68, 1.27)	1.00 (0.73, 1.36)	1.08 (0.78, 1.48)
Secondary	14,278	6.8	6.1	5.9	0.89 (0.75, 1.05)	0.86 (0.73, 1.02)	0.97 (0.82, 1.16)
Primary school or lower	278	12.4	3.0	6.8	**0.16 (0.04, 0.71)**	0.38 (0.12, 1.24)	2.36 (0.52, 10.65)
Hemoglobin level at first prenatal visit							
<13.2 g/dL	13,945	6.8	5.8	6.3	0.81 (0.72, 1.01)	0.95 (0.80, 1.12)	1.11 (0.97, 1.32)
≥13.2 g/dL	3825	8.3	8.3	6.1	0.96 (0.72, 1.28)	**0.69 (0.51, 0.93)**	**0.71 (0.52, 0.96)**
Mild anemia	1000	8.5	6.7	8.7	0.81 (0.45, 1.44)	1.09 (0.62, 1.93)	1.37 (0.76, 2.48)
20–24 years	746	9.6	6.2	9.0	0.71 (0.36, 1.38)	1.04 (0.55, 1.98)	1.52 (0.76, 3.02)

Bold indicate $p < 0.05$.

FA, folic acid; IFA, iron–folic acid; MMN, multiple micronutrient; BMI, body mass index; PIH, pregnancy-induced hypertension; AOR, adjusted odds ratio; 95% CI, 95% Confidential interval.

[a]PIH was defined as any occurrence of either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg starting at or after 20 weeks of gestation among women with previously normal blood pressure prior to 20 weeks.

[b]Adjusted for maternal age, gestational age at enrollment, BMI at first prenatal visit, hemoglobin level at first prenatal visit, compliance of supplementation, education, occupation, ethnicity except for the stratified factor.